Antispasmodics.

II, III, and IV

A DISSERTATION

SUBMITTED TO THE HORACE H. RACKHAM SCHOOL OF GRADUATE
STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE UNIVERSITY OF MICHIGAN

By
Ferdinand B. Zienty
1938

[Reprinted from the Journal of the American Chemical Society, 61, 93–95 and 771–776 (1939).]

R. UNIV.
BIBLIOTHEEK
LEIDEN

[Reprinted from the Journal of the American Chemical Society, 61, 93–95 and 771–776 (1939).]

[Contribution from the College of Pharmacy, University of Michigan]

Antispasmodics. II[1]

By F. F. Blicke and F. B. Zienty[2]

Since no extensive, systematic study seems to have been published which might permit some conclusion to be reached relative to a relationship between chemical structure and antispasmodic activity, we have prepared a large number of amines which have been tested pharmacologically, usually in the form of their hydrochlorides, by Dr. C. W. Geiter in the Frederick Stearns and Company Laboratories.

It cannot be stressed too emphatically that no trustworthy, broad generalization can be drawn except on the basis of data obtained from the examination of hundreds of compounds. However, as far as the amines described in this and the preceding paper[3] are concerned, the following statements may be made from the data now available.

An examination of the cyclohexylalkyl compounds of the series $CH_3N[(CH_2)_x\text{-}C_6H_{11}]_2$ in which $x = 1, 2, 3$ or 4 showed that all of the compounds appear to be weak in activity except methyldi-β-cyclohexylethylamine, $CH_3N[(CH_2)_2\text{-}C_6H_{11}]_2$, which is a strong antispasmodic.

A second series may be represented by the general formula $RN(CH_2\text{-}CH_2\text{-}C_6H_{11})_2$ in which R = hydrogen, methyl, ethyl, propyl, isopropyl, butyl, amyl, heptyl, phenyl, β-cyclohexylethyl, allyl, cyclohexyl, benzyl or β-hydroxyethyl. The first five compounds in this group were found to be

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Monroe, *J. Am. Chem. Soc.*, **61**, 91 (1939).

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides of the amines were recrystallized as follows: compounds 24, 28 and 29 were recrystallized from carbon tetrachloride; compounds 14, 25 and 26 from 1,4-dioxane; compounds 4, 7 and 12 from ethyl acetate; compound 5 from acetone; compound 11 from alcohol; compound 9 from a mixture of absolute alcohol and ethyl acetate; compounds 1, 2, 6 and 10 from a mixture of alcohol and acetone; compound 13 from a mixture of acetone and petroleum ether (30–40°); compounds 3, 8, 15, 16 and 27 were precipitated from a carbon tetrachloride solution by addition of dry ether; compound 30 was precipitated from an alcohol solution by addition of dry ether; the chloroaurate of compound 21 was recrystallized from dilute alcohol.

	Amine (secondary)	Antispasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	%Cl Calcd.	Found
1	Methylcyclohexylmethyl	(Stimulant)	Methylamine	65–66	13	193–194	$C_8H_{18}NCl$	21.67	21.53
2	Ethylcyclohexylmethyl	(Stimulant)	Ethylamine	72–73	12	249–250	$C_9H_{20}NCl$	19.96	19.87
3	β-Hydroxyethyl-β′-cyclohexylethyl	Inactive	β-Hydroxyethylamine	138–142	7	163–164	$C_{10}H_{22}ONCl$	17.08	16.94
4	Propyl-β-cyclohexylethyl	(Stimulant)	Propylamine	106–107	13	266–267	$C_{11}H_{24}NCl$	17.24	17.10
5	Isopropyl-β-cyclohexylethyl	Weak	Isopropylamine	102–104	16	199–200	$C_{11}H_{24}NCl$	17.24	17.02
6	Amyl-β-cyclohexylethyl	Weak	Amylamine	109–115	7	265–266	$C_{13}H_{28}NCl$	15.17	15.09
7	Heptyl-β-cyclohexylethyl	Active	Heptylamine	135–140	7	242–243	$C_{15}H_{32}NCl$	13.55	13.47
8	Phenyl-β-cyclohexylethyl	Weak	Aniline	170–173	9	122–123	$C_{14}H_{22}NCl$	14.79	14.71
9	Di-β-cyclohexylethyl	Active	β-Cyclohexylethylamine[a]	168–173	8	245–246	$C_{16}H_{32}NCl$	12.95	12.65
10	α-Cyclohexylethyl-β′-cyclohexylethyl	Active	α-Cyclohexylethylamine[b]	165–166	10	222–223	$C_{16}H_{32}NCl$	12.95	12.87
11	Di-α-cyclohexylethyl[c]	Weak	...	140–142	4	304–305	$C_{16}H_{32}NCl$	12.95	12.93
	Amine (tertiary)								
12	Methyldicyclohexyl	Weak	Dicyclohexylamine	131–133	13[d]	193–194	$C_{13}H_{26}NCl$	15.30	15.14
13	Amyldicyclohexyl	Weak	Dicyclohexylamine	178–181	20	113–114	$C_{17}H_{34}NCl$	12.32	12.31
14	Methyldicyclohexylmethyl	Weak	Methylamine	124–125	4	240–241	$C_{15}H_{30}NCl$	13.66	13.55
15	Ethyldicyclohexylmethyl	(Stimulant)	Ethylamine	149–153	12	137–138	$C_{16}H_{32}NCl$	12.95	12.90
16	β-Hydroxyethyldi-β′-cyclohexylethyl	Inactive	β-Hydroxyethylamine	190–193	5	112–113	$C_{18}H_{36}ONCl$	11.16	11.22
17	Di-β-hydroxyethyl-β′-cyclohexylethyl	Inactive	Di-β-hydroxyethylamine	177–179	7	Oil[e]	...	...	...
18	Propyldi-β-cyclohexylethyl	Active	Propylamine	160–165	7	Oil	$C_{19}H_{37}N$	N,[f] 5.02	4.96
19	Isopropyldi-β-cyclohexylethyl	Active	Isopropylamine	171–174	7	Oil	$C_{19}H_{37}N$	N,[f] 5.02	5.24
20	Butyldi-β-cyclohexylethyl	Weak	Butylamine	176–178	7	Oil	$C_{20}H_{39}N$	N,[f] 4.78	4.68
21	Dibutyl-β-cyclohexylethyl	Weak	Dibutylamine	124–127	5	127–128[g]	$C_{16}H_{34}NCl_4Au$	Au, 34.04	34.01
22	Amyldi-β-cyclohexylethyl	Weak	Amylamine	178–181	7	Oil	$C_{21}H_{41}N$	N,[f] 4.56	4.70
23	Heptyldi-β-cyclohexylethyl	Inactive	Heptylamine	197–202	6	Oil	$C_{23}H_{45}N$	N,[f] 4.18	4.21
24	Allyldi-β-cyclohexylethyl	(Stimulant)	Allylamine	170–172	5	137–138	$C_{19}H_{36}NCl$	11.30	11.31
25	Cyclohexyldi-β-cyclohexylethyl	(Stimulant)	Cyclohexylamine	190–193	5	166–167	$C_{22}H_{42}NCl$	9.97	10.09
26	Dicyclohexyl-β-cyclohexylethyl	Active	Dicyclohexylamine	180–182	5	172–173	$C_{29}H_{38}NCl$	10.82	10.83
27	Phenyldi-β-cyclohexylethyl	Weak	Aniline	213–218	5	149–150	$C_{22}H_{36}NCl$	10.14	9.94
28	Benzyldi-β-cyclohexylethyl	(Stimulant)	Benzylamine	207–210	5	142–143	$C_{23}H_{38}NCl$	9.75	9.73
29	Tri-β-cyclohexylethyl	Weak	Compound 9	200–208	6	233–234	$C_{24}H_{46}NCl$	9.24	9.26
30	Methyldi-α-cyclohexylethyl	Weak	Compound 11	167–169	12	179–180	$C_{17}H_{34}NCl$	12.32	12.40

[a] Coleman and Adams, *J. Am. Chem. Soc.*, **54**, 1983 (1932). [b] Leithe, *Ber.*, **65**, 665 (1932). [c] Obtained as a by-product in the preparation of the corresponding primary amine. [d] Prepared by different methods Skita and Berendt [*Ber.*, **52**, 1528 (1919)] reported 265°; Hiers and Adams [*ibid.*, **59**, 167, 170 (1926)] found 140–141° (26 mm.). [e] The hydrochloride of the dibenzoate is described above. [f] Analysis of the base. [g] Melting point of the chloroaurate.

active,[4] the butyl and amyl derivatives weakly active and the heptyl compound inactive; the phenyl and β-cyclohexylethyl derivatives are weak antispasmodics; the allyl, cyclohexyl and benzyl compounds are stimulants and the β-hydroxyethyldi-β′-cyclohexylethylamine is inactive.

In a series of secondary amines which conform to the general formula $RN(H)(CH_2\text{-}CH_2\text{-}C_6H_{11})_2$ in which R = propyl, isopropyl, amyl, heptyl, phenyl, β-cyclohexylethyl or α-cyclohexylethyl only the heptyl, β-cyclohexylethyl and α-cyclohexylethyl compounds are active.

Dicyclohexylamine, methyl- and amyldicyclohexylamine exhibit weak activity but β-cyclohexylethyldicyclohexylamine is decidedly active.

A few compounds of the type $CH_3N(CH_2\text{-}CH_2\text{-}R)_2$ were prepared in which R represents phenyl, phenoxymethyl, cyclopentyl or benzoyl; the first two compounds proved to be active, the last two weak.

It is interesting to compare the activity of an amine which contains an α-cyclohexylethyl group with that of an isomeric β-cyclohexylethyl com-

(4) In this series of papers the term active is used to denote that the compound is a strong antispasmodic and the term inactive to indicate a very low degree of activity.

pound. Di-α-cyclohexylethylamine was found to be weak while di-β-cyclohexylethylamine is active; the mixed amine α-cyclohexylethyl-β′-cyclohexylethylamine is active. Furthermore, methyldi-α-cyclohexylethylamine is weak while the isomeric methyldi-β-cyclohexylethylamine is active.

Experimental Part

The amines, except those described below, were prepared by the general methods outlined previously.[3]

β-Cyclohexylethyl Alcohol.—Several modifications have been made in the procedure of Hiers and Adams.[5]

Cyclohexylmagnesium bromide was prepared from 72 g. of magnesium, 489 g. of bromocyclohexane and 1000 cc. of ether in a 3-liter three-necked flask fitted with a stirrer, condenser and dropping funnel. The solution of the Grignard reagent was stirred, cooled to 15–20° and maintained at this temperature while 220 cc. of liquid ethylene oxide was added dropwise. The temperature of the mixture was then allowed to rise to that of the room, 500 cc. of dry benzene was added, the mixture heated to 70°, maintained at this temperature for one hour and then treated with ice and sulfuric acid. The product which boiled at 105–110° (20 mm.) was used; yield 197 g. or 51% of the calcd. amount.

Methyldicyclohexylamine (No. 12).—A mixture of 18.1 g. of dicyclohexylamine and 15 g. of 38% formaldehyde solution was heated on a steam-bath for ten hours. The amine was extracted with ether, the extract dried and the solvent removed; yield of pure product 16 g.

Hydrochloride of the Dibenzoyl Derivative of Di-β-hydroxyethyl-β′-cyclohexylethylamine.—To 4.3 g. of di-β-hydroxyethyl-β′-cyclohexylethylamine (compound 17), dissolved in 10 g. of pyridine, there was added 5.6 g. of benzoyl chloride dissolved in 10 cc. of benzene. The mixture was refluxed for one hour on a steam-bath, filtered, the solvents removed, the oily residue washed with water and then extracted with ether. The extract was dried and treated with hydrogen chloride whereupon the hydrochloride precipitated. The oily hydrochloride was washed with absolute ether, dissolved in a small amount of ethyl acetate and precipitated by the addition of dry ether; the oily precipitate soon crystallized. It was dissolved in 50% alcohol and the solvents allowed to evaporate partially at ordinary temperature; m. p. 137–138°.

Anal. Calcd. for $C_{26}H_{34}O_4NCl$: Cl, 7.71. Found: Cl, 7.84.

α-Cyclohexylethylamine.—A mixture of 126 g. of methyl cyclohexyl ketone[6] and 189 g. of ammonium formate was placed in a 500-cc. Claisen flask, attached to an inclined condenser, and a few pieces of porous plate added. The mixture was heated with a thermometer immersed in the liquid. When the temperature reached 120° practically all of the formate had melted, two layers were formed and the mixture foamed slightly. The foaming increased as the temperature was raised. At 140° water and methyl cyclohexyl ketone began to distil. The material became homogeneous at 155°. When the mixture reached a temperature of 180° the heating was interrupted and the upper ketone layer in the distillate was separated and returned to the Claisen flask. The mixture was heated at 180–185° until distillation of the ketone became slow. The ketone which had distilled into the receiver was again returned to the Claisen flask and the mixture heated three hours longer.

The material was cooled, washed with about 200 cc. of water and returned to the reaction flask. The wash water was extracted three times with 30-cc. portions of benzene and the extracts poured into the reaction flask. After the addition of 125 cc. of concd. hydrochloric acid heat was applied gradually until the benzene was removed, the mixture boiled for one hour, cooled and extracted with benzene to remove unchanged ketone. Excess alkali was added, the oil extracted with ether, the extract dried with fused sodium sulfate and the solvent removed; b. p. 66–67° (14 mm.).[7]

The hydrochloride precipitated when hydrogen chloride was passed into an ether solution of the base; m. p. 237–238°[8] after recrystallization from a mixture of alcohol and acetone. The salt is very soluble in water.

Anal. Calcd. for $C_8H_{18}NCl$: Cl, 21.67. Found: Cl, 21.52.

Di-α-cyclohexylethylamine (No. 11).—In the preparation of the primary amine described above there was obtained 23 g. of di-α-cyclohexylethylamine.

The hydrochloride precipitated when an ether solution of the base was treated with hydrogen chloride. The salt is not very soluble in water.

Methyldi-α-cyclohexylethylamine (No. 30).—Seven grams of di-α-cyclohexylethylamine hydrochloride, ten drops of concd. hydrochloric acid and 7.5 g. of formalin were refluxed for ten hours, the mixture made alkaline and extracted with ether. The solvent was removed from the dried extract and the residue distilled; b. p. 167–169° (12 mm.); yield 4.6 g.

The hydrochloride, obtained in the manner described above, is very soluble in water.

Summary

A number of secondary and tertiary amines have been prepared which contain alkyl, cyclohexyl, α-cyclohexylethyl or β-cyclohexylethyl groups. Some of these compounds have been found to be strong antispasmodics.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 5, 1938

(5) Hiers and Adams, *J. Am. Chem. Soc.*, **48**, 1091 (1926).

(6) Bouveault, *Bull. soc. chim.*, [3] **29**, 1050 (1903).

(7) Leithe [*Ber.*, **65**, 665 (1932)] prepared the amine by hydrogenation of α-phenylethylamine and Wallach [*Ann.*, **389**, 192 (1912)] by reduction of the nitrosochloride of ethylidenecyclohexane but neither investigator reported a boiling point.

(8) Leithe[7] reported 242°.

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. III[1]

BY F. F. BLICKE AND F. B. ZIENTY[2]

It has been found that methyldi-β-cyclohexylethylamine, $CH_3N(CH_2—CH_2—C_6H_{11})_2$, and certain other closely related cycloalkylalkylamines are strong antispasmodics.[3,4] Since the cyclohexyl group is aliphatic rather than aromatic in character we wished to determine whether or not antispasmodic activity might be found among the saturated, strictly aliphatic amines, particularly in such a compound as methyldi-*n*-octylamine since this substance contains two saturated carbon chains which correspond to those which would be formed if the cyclohexyl rings in methyldi-β-cyclohexylethylamine were ruptured between the ring carbon atoms 1 and 2. Consequently, there was prepared methyldi-*n*-octylamine, methyldi-*n*-hexylamine and also methyldi-2-ethylhexylamine and methyldi-2-ethylbutylamine (Table I). Methyldi-*n*-octyl- and methyldi-*n*-hexylamine proved to be weak in activity while the other two amines exhibited such a low order of potency that they have been listed as inactive.

It was of interest to prepare and compare the activity of the four compounds ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyldi-β-cyclopentylethylamine with the corresponding four cyclohexylamines which have been described previously, namely, ethyl-, *n*-propyl-, *n*-butyl- and *n*-amyldi-β-cyclohexylethylamine. In the cyclopentyl series only the *n*-amyl compound was found to be a strong antispasmodic, whereas among the cyclohexyl compounds only the ethyl and propyl derivatives exhibited strong activity.

No active antispasmodics were found among the seven heterocyclic amines which contained the morpholine, piperazine or α-furfuryl ring.

Methyldi - 2 - methylcyclohexylmethyl- and methyldi-3-cyclohexylmethylamine, two closely related isomers of methyldi-β-cyclohexylethylamine, were prepared (Table II). The 2-methylcyclohexylmethyl compound proved to be a weak antispasmodic and the 3-methylcyclohexylmethylamine possessed so little activity that it has been described as inactive.

The next higher homolog of the last mentioned amine, that is, methyldi-β-3-methylcyclohexylethylamine, proved to be active; methyldi-β-4-methylcyclohexylethylamine also was found to be an active amine.

Since ethyl- and propyldi-β-phenylethylamine, as well as ethyl- and propyldi-β-cyclohexylethylamine, are strong antispasmodics, it can be seen that, at least in some instances, phenyl can be substituted for cyclohexyl without loss of activity. Another illustration of this is found in the strong antispasmodic ethyl-β-cyclohexylethyl-β′-phenylethylamine.

Ethyl - β - cyclohexylethylcyclohexylmethylamine, an isomer of methyldi-β-cyclohexylethylamine, is an active compound.

By the introduction of methyl and β-cyclohexylethyl groups into ethylenediamine and trimethylenediamine (compounds 17 and 18, Table II) these two diamines were converted into substances which possessed marked antispasmodic properties.

Experimental Part

Alcohols.—2-Methylcyclohexylmethyl,[5] b. p. 76–77° at 18 mm., 3-methylcyclohexylmethyl,[5] b. p. 75–76° at 6 mm., β-(3-methylcyclohexyl)-ethyl, b. p. 86–88° at 5 mm. and β-(4-methylcyclohexyl)-ethyl alcohol, b. p. 85–87° at 6 mm., were prepared by treatment of the substituted cyclohexylmagnesium bromide with formaldehyde or ethylene oxide according to a slight modification[6] of the method used by Hiers and Adams[7] for the preparation of β-cyclohexylethyl alcohol.

α-Cyclohexylethyl alcohol was obtained from cyclohexylmagnesium bromide and acetaldehyde.[8]

Cyclopentanol was prepared by reduction of cyclopentanone with sodium and a mixture of one part of methyl alcohol, one part of ether and two parts of water.[9] It is claimed that methyl alcohol reduces the amount of

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) (a) Blicke and Monroe, *J. Am. Chem. Soc.*, **61**, 91 (1939); (b) Blicke and Zienty, *ibid.*, **61**, 93 (1939).

(4) All of the pharmacological data have been determined by Dr. C. W. Geiter in the Laboratories of Frederick Stearns and Company.

(5) This alcohol has been obtained by a different procedure by Skita and Schonfelder, *Ann.*, **431**, 20, 29 (1923).

(6) Ref. 3 (b).

(7) Hiers and Adams, *J. Am. Chem. Soc.*, **48**, 1091 (1926); see also "Organic Syntheses," Coll. Vol. I, 1932, p. 182.

(8) Bouveault (*Bull. soc. chim.*, [3] **29**, 1050 (1903)) and Zelinsky, (*ibid.*, [4] **2**, 1122 (1907)) used cyclohexylmagnesium chloride.

(9) Nenitzescu and Ionescu, *Bull. soc. chim. Romania*, **14**, 65 (1932); *C. A.*, **27**, 1329 (1933).

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 1, 2, 3, 4 and 17 from acetone; compounds 10, 11 and 24 from alcohol; compounds 7, 13 and 15 from 1,4-dioxane; compound 25 and the chloroaurates of compounds 19 and 20 from dilute alcohol; compound 26 from methyl alcohol; compounds 18, 27 and 28 and the chloroaurate of compound 14 were precipitated from an acetone solution by the addition of dry ether; compound 12 was precipitated from a carbon tetrachloride solution by the addition of dry ether; compound 23 was precipitated from a chloroform solution by the addition of acetone.

	Amine (secondary)	Anti-spasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	Found
1	Methylhexyl	Inactive	Methylamine	140–142	735	178–179	$C_7H_{18}NCl$	23.39	23.51
2	Methyl-2-ethylbutyl	Inactive	Methylamine	128–129	742	201–202	$C_7H_{18}NCl$	23.39	23.49
3	Methyl-2-ethylhexyl	Inactive	Methylamine	73–75	15	185–186	$C_9H_{22}NCl$	19.73	19.58
4	Methyloctyl	Weak	Methylamine	78–79	14	180–181	$C_9H_{22}NCl$	19.73	19.70
5	Methyl-2-octyl	Weak	Methylamine	70–71	14	Oil	$C_9H_{21}N$	N, 9.78	9.64
6	Ethyl-β-cyclopentylethyl	Inactive	Ethylamine	73–74	13	197–198	$C_9H_{20}NCl$	19.96	20.24
7	Propyl-β-cyclopentylethyl	Inactive	Propylamine	72–74	5	251–253	$C_{10}H_{22}NCl$	18.50	18.36
8	Butyl-β-cyclopentylethyl	Inactive	Butylamine	106–107	13	278–279	$C_{11}H_{24}NCl$	17.24	17.26
9	Amyl-β-cyclopentylethyl	Inactive	Amylamine	98–100	4	284–285	$C_{12}H_{26}NCl$	16.14	16.28
10	Dicyclohexyl	Weak	.....	.....	...	326–327[a]	.....	...	...
11	β-Cyclohexylethyl-γ′-cyclohexylpropyl	Weak	β-Cyclohexylethylamine[b]	150–156	6	322–323	$C_{17}H_{34}NCl$	12.32	12.34
	Amine (tertiary)								
12	Methyldihexyl	Weak	Methylamine	121–122	19	144–145	$C_{13}H_{30}NCl$	15.04	15.00
13	Methyldi-2-ethylbutyl	Inactive	Methylamine	100–101	13	154–155	$C_{13}H_{30}NCl$	15.04	14.87
14	Methyldi-2-ethylhexyl	Inactive	Methylamine	113–114	6	103–104*	$C_{17}H_{38}NCl_4Au$	Au, 33.12	33.15
15	Methyldioctyl	Weak	Methylamine	136–138	5	149–150	$C_{17}H_{38}NCl$	12.15	12.18
16	Methyldi-β-hydroxyethyl	(Stimulant)	Methylamine	141–142	18[c]	.....	.....	...	...
17	Methyldi-β-chloroethyl	Inactive	Compound 16	.....	...	113–114[d]	$C_5H_{12}NCl_3$	55.26	55.14
18	Ethyldi-β-cyclopentylethyl	Weak	Ethylamine	140–145	7	115–116	$C_{16}H_{32}NCl$	12.95	13.42
19	Propyldi-β-cyclopentylethyl	Weak	Propylamine	147–150	7	145–146*	$C_{17}H_{34}NCl_4Au$	Au, 33.35	33.37
20	Butyldi-β-cyclopentylethyl	Weak	Butylamine	153–158	6	133–134*	$C_{18}H_{36}NCl_4Au$	Au, 32.58	32.66
21	Amyldi-β-cyclopentylethyl	Active	Amylamine	163–168	5	Oil	$C_{19}H_{37}N$	N, 5.02	4.77
22	N-Butylmorpholine	(Stimulant)	Morpholine	67–68	10	213–214	$C_8H_{18}ONCl$	19.74	19.59
23	N-Cyclohexylmorpholine[e]	(Stimulant)	Morpholine	111–112	12	254–255	$C_{10}H_{20}ONCl$	17.24	17.07
24	N-β-Cyclohexylethylmorpholine	(Stimulant)	Morpholine	132–134	12	260–261	$C_{12}H_{24}ONCl$	15.17	15.09
25	Methyldi-β-N-morpholylethyl	Inactive	Morpholine and compound 17	161–164	8	277–278[f]	$C_{18}H_{30}O_2N_3Cl_3$	29.01	29.30
26	N,N′-Di-β-cyclohexylethylpiperazine	Weak	β-Cyclohexylethylamine	.....	...	325–326[g]	$C_{20}H_{40}N_2Cl_2$	18.70	18.73
27	Methylcyclohexylmethyl-α-furfuryl	Weak	Methyl-α-furfurylamine[h]	103–105	5	107–108	$C_{13}H_{22}ONCl$	14.55	14.49
28	Methyl-β-cyclohexylethyl-α-furfuryl	Weak	Methyl-α-furfurylamine	121–123	5	163–164	$C_{14}H_{24}ONCl$	13.68	13.78

[a] Willstätter and Hatt (*Ber.*, **45**, 1476 (1912)) stated that the compound sublimes at 300–315°. Winans and Adkins (*J. Am. Chem. Soc.*, **54**, 310 (1932)) reported the melting point to be 333°. [b] Coleman and Adams, *ibid.*, **54**, 1983 (1932). [c] Knorr and Matthes (*Ber.*, **31**, 1069 (1898)) reported the boiling point to be 246–248°. [d] Prelog and Stepan (*Coll. Czech. Chem. Comm.*, **7**, 93 (1935); *C. A.*, **29**, 4013 (1935)) stated the melting point to be 116–117°. [e] This compound is mentioned in the French Patent 711,560, *Chem. Zentr.*, **103**, I, 2998 (1932); in the English Patent 362,061, *Chem. Zentr.*, **103**, I, 3502 (1932), and by Carswell and Morrill, *Ind. Eng. Chem.*, **29**, 1248 (1937), but the analysis and properties were not recorded. [f] Trihydrochloride. [g] Dihydrochloride. [h] Schwabbauer, *Ber.*, **35**, 410 (1902); von Braun and Köhler, *ibid.*, **51**, 86 (1918). * M. p. of chloroaurate.

pinacol formed in the ordinary reduction procedure in which alcohol is not used.[10]

Bromides.—The 2-, 3- and 4-methylcyclohexylalkyl bromides were prepared by the action of phosphorus tribromide (20% excess) on the corresponding alcohols: 2-methylcyclohexylmethyl bromide, b. p. 74–76° at 10 mm.; 3-methylcyclohexylmethyl bromide, b. p. 71–73° at 7 mm.; β-(3-methylcyclohexyl)-ethyl bromide, b. p. 79–81° at 5 mm.; β-(4-methylcyclohexyl)-ethyl bromide, b. p. 78–79° at 8 mm.

α-Cyclohexylethyl bromide was obtained when dry hydrogen bromide was passed into 372 g. of α-cyclohexylethyl alcohol, dissolved in 200 cc. of benzene, until no further formation of water was evident. After several hours the benzene layer was separated, dried with calcium chloride, the solvent removed and the residue distilled. The distillate was shaken twice with 100-cc. portions of concd. sulfuric acid and then distilled again; b. p. 94–96° under 26 mm. pressure; yield 330 g. or 59% of the calcd. amount.

Anal. Calcd. for $C_8H_{15}Br$: Br, 41.83. Found: Br, 41.87.

Amines.—The amines were synthesized by the general methods outlined previously [11]

All of the amine hydrochlorides listed in Table I were

(10) In the attempted reduction of dimethyl sebacate with sodium, water and ether almost all of the ester was recovered unchanged. However, when the ester was treated with sodium in the presence of a mixture of water and ether which contained 15–20% of methyl alcohol a 65% yield of decamethylene glycol was obtained.

(11) Ref. 3a.

TABLE II

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 1, 2, 3, 4, 9, 10, 12 and 13 from acetone; compounds 5, 17 and 18 from absolute alcohol; compound 6 from dilute alcohol; compounds 7 and 8 from 1,4-dioxane; compounds 15 and 16 from carbon tetrachloride; compounds 11 and 14 were precipitated from acetone solution by the addition of dry ether.

	Amine (secondary)	Antispasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	Found
1	Methyl-2-methylcyclohexylmethyl	Inactive	Methylamine	57–61	7	230–231	$C_9H_{20}NCl$	19.96	20.25
2	Methyl-3-methylcyclohexylmethyl	Inactive	Methylamine	58–60	6	182–184	$C_9H_{20}NCl$	19.96	19.96
3	Methyl-β-3-methylcyclohexylethyl	Inactive	Methylamine	74–75	8	162–163	$C_{10}H_{22}NCl$	18.50	18.42
4	Methyl-β-4-methylcyclohexylethyl	Weak	Methylamine	81–82	9	162–163	$C_{10}H_{22}NCl$	18.50	18.64
5	N-β-Cyclohexylethylethylenediamine	(Stimulant)	Ethylenediamine	115–120	8	About 305[a] (dec.)	$C_{10}H_{24}N_2Cl_2$	29.16	29.11
6	N,N′-Di-β-cyclohexylethylethylenediamine	Weak	Ethylenediamine	195–200	8	319–320[a]	$C_{18}H_{38}N_2Cl_2$	20.07	19.97
	Amine (tertiary)								
7	Methyldi-2-methylcyclohexylmethyl	Weak	Methylamine	.....	..	188–189	$C_{17}H_{34}NCl$	12.32	12.35
8	Methyldi-3-methylcyclohexylmethyl	Inactive	Methylamine	135–140	7	205–206	$C_{17}H_{34}NCl$	12.32	12.37
9	Methyldi-β-3-methylcyclohexylethyl	Active	Methylamine	158–161	7	228–229	$C_{19}H_{38}NCl$	11.23	11.14
10	Methyldi-β-4-methylcyclohexylethyl	Active	Methylamine	166–170	9	241–242	$C_{19}H_{38}NCl$	11.23	11.23
11	Ethyldi-β-phenylethyl	Active	Ethylamine	176–178	7[b]	136–137[c]	.....	...	...
12	Propyldi-β-phenylethyl	Active	Propylamine	170–172	6	158–159	$C_{19}H_{26}NCl$	11.68	11.79
13	Butyldi-β-phenylethyl	Weak	Butylamine	194–195	9	140–141	$C_{20}H_{28}NCl$	11.16	11.13
14	Ethyl-β-cyclohexylethyl-cyclohexylmethyl	Active	Ethylcyclohexylmethylamine[d]	146–149	5	116–117	$C_{17}H_{34}NCl$	12.32	12.42
15	Ethyl-β-cyclohexylethyl-β′-phenylethyl	Active	Ethyl-β-phenylethylamine[e]	163–168	7	117–118	$C_{18}H_{30}NCl$	11.99	11.75
16	Butyl-β-cyclohexylethyl-β′-phenylethyl	Weak	Butyl-β-phenylethylamine[f]	180–182	6	128–129	$C_{20}H_{34}NCl$	10.96	11.02
17	N,N′-Dimethyl-N,N′-di-β-cyclohexylethylethylenediamine	Active	Methyl-β-cyclohexylethylamine[g]	180–182	9	276–277[a]	$C_{20}H_{42}N_2Cl_2$	18.60	18.73
18	N,N′-Dimethyl-N,N′-di-β-cyclohexylethyltrimethylenediamine	Active	Methyl-β-cyclohexylethylamine	190–195	5	294–295[a]	$C_{21}H_{44}N_2Cl_2$	17.95	17.86

[a] Dihydrochloride. [b] Külz and Rosenmund (German Patent 623,593, *Chem. Zentr.*, **107**, II, 1025 (1936)) reported 180–182° (2 mm.). [c] Külz and Rosenmund (ref. *b*) found 134° but in U. S. Patent 2,006,114 (*C. A.*, **29**, 5602 (1935)) reported as 137°. [d] Blicke and Zienty, THIS JOURNAL, **61**, 774 (1939). [e] Von Braun, *Ber.*, **43**, 3215 (1910). [f] Winans and Adkins, THIS JOURNAL, **54**, 310 (1932). [g] Blicke and Monroe, *ibid.*, **61**, 91 (1939).

prepared by treatment of an ether solution of the amine with hydrogen chloride except compounds 1, 2, 3, 4, 12, 13 and 15; in these instances the amine was dissolved in petroleum ether (30–40°).

The hydrochlorides of five of the amines in Table I were obtained as oils, hence in the case of compound 5 and compound 21 the corresponding bases were analyzed for nitrogen. The oily hydrochlorides of compounds 14, 19 and 20 were dissolved in water and excess hydrochloric acid added; upon addition of 5% gold chloride solution the chloroaurates precipitated. If the latter separated in an oily state they became crystalline after a short time.

In order to prepare the amine hydrochlorides mentioned in Table II, ether was used as a solvent for the bases except in the case of compound 14 and compound 16; petroleum ether was used for the former and a mixture of ether and petroleum ether for the latter.

Summary

Forty-six secondary and tertiary amines have been described. Many of the amines contain alkyl and cycloalkylalkyl or arylalkyl groups. Nine of these substances proved to be strong antispasmodics.

ANN ARBOR, MICHIGAN RECEIVED JANUARY 3, 1939

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Antispasmodics. IV[1]

BY F. F. BLICKE AND F. B. ZIENTY[2]

In this paper, a continuation of our studies of antispasmodics,[3] there has been described a number of mixed tertiary amines of the general formula CH_3NRR' in which R represents a β-cyclohexylethyl and R′ an alkyl, cycloalkylalkyl or arylalkyl group.

These compounds were prepared since it was of interest to determine the extent to which antispasmodic activity would be retained by the replacement of one of the β-cyclohexylethyl radicals in methyldi-β-cyclohexylethylamine by some other group. Methyldi-β-cyclohexylethylamine was chosen since this compound was found to be a strong antispasmodic early in our investigation.

Furthermore, we wished to obtain data with regard to the relative activities of the mixed amine, CH_3NRR', and the corresponding amines CH_3NR_2 and $CH_3NR'_2$. So far, six instances have been found in which the mixed amine exhibited strong activity while one or both of the amines of types CH_3NR_2 and $CH_3NR'_2$ proved to be weak antispasmodics.

From the data in Table I[4] it can be seen that active antispasmodics are obtained by the substitution of one β-cyclohexylethyl group in methyldi-β-cyclohexylethylamine by the *n*-octyl, cinnamyl, γ-cyclohexylpropyl, δ-cyclohexylbutyl or β-phenylethyl radical. Antispasmodics, weak in activity, are produced when one β-cyclohexylethyl group is replaced by a *n*-hexyl, 2-(6-methyl-5-heptenyl), cyclohexyl, cyclohexylmethyl, β-cyclopentylethyl, γ-phenoxypropyl or a benzyl radical.

However, if the carbon chain in the β-cyclohexylethyl radical is lengthened by one or two carbon atoms the cyclohexyl and cyclohexylmethyl groups may be used effectively; thus, the tertiary amines methylcyclohexyl-δ-cyclohexylbutyl, methylcyclohexylmethyl-δ-cyclohexylpropyl and methylcyclohexylmethyl-δ-cyclohexylbutylamine are strong antispasmodics.

(1) This article is part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by F. B. Zienty in partial fulfilment of the requirements for the degree of Doctor of Philosophy, in the University of Michigan.

(2) Frederick Stearns and Company Fellow.

(3) Blicke and Monroe, *J. Am. Chem. Soc.*, **61**, 91 (1939); Blicke and Zienty, *ibid.*, **61**, 93, 771 (1939).

(4) We are indebted to Dr. C. W. Geiter of Frederick Stearns and Company for the pharmacological evaluation of the amines.

Experimental Part

All of the amines, except those described below, were prepared by the general procedures described previously. The amine hydrochlorides were obtained by treatment of an ether solution of the base with hydrogen chloride.

Methyldicinnamylamine.—A mixture of 9.3 g. of methylamine, 70 cc. of alcohol, 35 cc. of benzene and 10.6 g. of anhydrous sodium carbonate was cooled and stirred and 19.7 g. of cinnamyl bromide, dissolved in 35 cc. of benzene, added from a dropping funnel. The material was heated for five hours on a steam-bath, the solvents removed and excess hydrochloric acid added to the residue. After the unchanged bromide had been extracted with ether, sodium hydroxide solution was added and the oily amines were dissolved in ether. The ether solution was dried with fused sodium sulfate and the solvent removed. Upon distillation there was obtained 5.0 g. of the tertiary amine, b. p. 180–185° at 5 mm., and 2.6 g. of methylcinnamylamine, b. p. 102–104° at 5 mm.[5]

The gummy, very hygroscopic hydrochloride of methyldicinnamylamine precipitated when hydrogen chloride was passed into an ether solution of the base. The product was washed with absolute ether and then dissolved in acetone. Upon addition of ether the hydrochloride precipitated as an oil which solidified after some time. The material was dissolved again in acetone and precipitated with ether. After this process had been repeated three times, crystalline hydrochloride was obtained. The latter becomes oily but does not dissolve when water is added to it.

Methyldi-2-cyclohexanonylmethylamine.—A mixture of 30 g. of trioxymethylene, 34 g. of methylamine hydrochloride, 196 g. of cyclohexanone and 200 cc. of alcohol was heated just to the boiling point; the reaction began and proceeded, vigorously, to completion without further application of heat. After about five minutes the trioxymethylene had disappeared. The solution was filtered, the alcohol removed, the residue cooled to about 30° and extracted with ether to remove cyclohexanone. The product was treated with 25% sodium hydroxide solution, the amines extracted with ether and the ether solution dried with fused sodium sulfate. After removal of the solvent the oily material was kept at 0° for twelve hours; absolute ether was added and the crystalline compound filtered; yield 14 g. Mannich and Braun[6] prepared the amine with the use of aqueous formaldehyde solution but obtained a yield of only 6 g. The base was recrystallized from methyl alcohol or benzene.

Hydrogen chloride was passed into a warm solution of 4 g. of the base in 125 cc. of benzene, the solvent decanted from the precipitated oily hydrochloride and dry ether added. The salt, which soon became crystalline, was purified by the gradual addition of anhydrous ether to 5 g. of the crude product dissolved in 20 cc. of absolute alcohol.

(5) Von Braun and Engel (*Ann.*, **436**, 313 (1924)) reported the boiling point to be 110–112° at 12 mm.

(6) Mannich and Braun, *Ber.*, **53**, 1877 (1920).

TABLE I

AMINES AND AMINE HYDROCHLORIDES

The hydrochlorides were recrystallized in the following manner: compounds 3, 7, 8, 9, 16, 17, 18 and 21 were recrystallized from acetone; compounds 4, 11, 12, 13, 14 and 20 from 1,4-dioxane; compound 6 from carbon tetrachloride; compound 15 from alcohol; compounds 1, 5, 10 and 19 from a mixture of acetone and alcohol; compound 2 was precipitated from an acetone solution by addition of dry ether. The chloroaurates of compounds 24 and 25 were recrystallized from dilute alcohol.

	Amine (tertiary)	Antispasmodic activity	Prepared from	B. p. of fraction used °C.	Mm.	Amine hydrochloride M. p., °C.	Formula	% Cl Calcd.	% Cl Found
1	Methyldibenzyl	(Stimulant)	Methylamine	161–162	12[a]	200–201[b]	$C_{15}H_{18}NCl$	14.32	14.33
2	Methyldicinnamyl	Weak	Methylamine	180–185	5	148–149	$C_{19}H_{22}NCl$	11.83	11.90
3	Methyl-cinnamyl-benzyl	Weak	Methylcinnamylamine[c]	175–180	10	141–142	$C_{17}H_{20}NCl$	12.96	13.01
4	Methyl-cinnamyl-γ-phenoxypropyl	Weak	Methylcinnamylamine	195–198	4	130–131	$C_{19}H_{24}ONCl$	11.16	11.19
5	Methyl-cinnamyl-cyclohexylmethyl	Inactive	Methylcinnamylamine	166–169	9	185–186	$C_{17}H_{26}NCl$	12.68	12.73
6	Methyl-cinnamyl-β-cyclohexylethyl	Active	Methyl-β-cyclohexylethylamine[d]	175–180	8	211–212	$C_{18}H_{28}NCl$	12.07	11.99
7	Methyl-cinnamyl-β-cyclopentylethyl	Weak	Methylcinnamylamine	164–167	8	183–184	$C_{17}H_{26}NCl$	12.68	12.73
8	Methyl-cyclohexyl-β-cyclohexylethyl	Weak	Methylcyclohexylamine[e]	133–137	6	201–202	$C_{15}H_{30}NCl$	13.66	13.55
9	Methyl-cyclohexyl-δ-cyclohexylbutyl	Active	Methylcyclohexylamine	151–155	4	184–185	$C_{17}H_{34}NCl$	12.32	12.30
10	Methyl-cyclohexylmethyl-β-cyclohexylethyl	Weak	Methyl-β-cyclohexylethylamine	144–146	6	250–251	$C_{16}H_{32}NCl$	12.95	12.91
11	Methyl-cyclohexylmethyl-γ-cyclohexylpropyl	Active	Methylcyclohexylmethylamine[f]	140–145	6	199–200	$C_{17}H_{34}NCl$	12.32	12.29
12	Methyl-cyclohexylmethyl-δ-cyclohexylbutyl	Active	Methylcyclohexylmethylamine	154–157	6	179–180	$C_{18}H_{36}NCl$	11.74	11.94
13	Methyl-β-cyclohexylethyl-hexyl	Weak	Methyl-β-cyclohexylethylamine	113–117	5	203–204	$C_{15}H_{32}NCl$	13.55	13.51
14	Methyl-β-cyclohexylethyl-octyl	Active	Methyl-β-cyclohexylethylamine	139–141	5	170–171	$C_{17}H_{36}NCl$	12.24	12.19
15	Methyl-β-cyclohexylethyl-benzyl	Weak	Methyl-β-cyclohexylethylamine	140–142	4	242–243	$C_{16}H_{26}NCl$	13.24	13.19
16	Methyl-β-cyclohexylethyl-β′-phenylethyl	Active	Methyl-β-cyclohexylethylamine	150–152	4	205–206	$C_{17}H_{28}NCl$	12.58	12.54
17	Methyl-β-cyclohexylethyl-γ′-phenoxypropyl	Weak	Methyl-β-cyclohexylethylamine	168–171	5	142–143	$C_{18}H_{30}ONCl$	11.37	11.38
18	Methyl-β-cyclohexylethyl-β′-cyclopentylethyl	Weak	Methyl-β-cyclohexylethylamine	137–139	6	251–252	$C_{16}H_{32}NCl$	12.95	13.11
19	Methyl-β-cyclohexylethyl-2-methylcyclohexyl-methyl	Inactive	Methyl-β-cyclohexylethylamine	137–139	5	230–231	$C_{17}H_{34}NCl$	12.32	12.33
20	Methyl-β-cyclohexylethyl-γ′-cyclohexylpropyl	Active	Methyl-β-cyclohexylethylamine	153–156	6	228–229	$C_{18}H_{36}NCl$	11.75	11.79
21	Methyl-β-cyclohexylethyl-δ′-cyclohexylbutyl	Active	Methyl-δ-cyclohexylbutylamine[g]	160–165	4	191–192	$C_{19}H_{38}NCl$	11.16	11.38
22	Methyl-β-cyclohexylethyl-2-(6-methyl-5-heptenyl)-	Weak	Methyl-2-(6-methyl-5-heptenyl)-amine[h]	140–145	5	Oil	$C_{17}H_{33}N$	N, 5.58	5.38
23	Methyl-β-hydroxyethyl-β′-(β″-cyclohexyl-ethoxy)-ethyl	Weak	Methyldi-β-hydroxyethylamine[i]	142–143	5	Oil	$C_{13}H_{27}O_2N$	N, 6.12	6.28
24	Methyldi-γ-phenylpropyl	Active	Methylamine	182–184	6	127–128[j]	$C_{19}H_{26}NCl_4Au$	Au, 32.47	32.37
25	Methyldi-δ-phenylbutyl	Active	Methylamine	193–195	6	113–114[j]	$C_{21}H_{30}NCl_4Au$	Au, 31.04	31.00
26	Methyldi-2-cyclohexanonylmethyl	Weak	Methylamine	(M. p. 170–172[i])		195–197[k]	$C_{15}H_{26}O_2NCl$	12.32	12.04

[a] Wegler and Frank (*Ber.*, **69**, 207 (1936)) reported 165° (15 mm.). [b] Hughes and Ingold (*J. Chem. Soc.*, 75 (1933)) described the hydrobromide and picrate. [c] Von Braun and Engel, *Ann.*, **436**, 312 (1924). [d] Blicke and Monroe, *J. Am. Chem. Soc.*, **61**, 92 (1939). [e] Sabatier and Mailhe, *Compt. rend.*, **153**, 1207 (1911). [f] Blicke and Zienty, *J. Am. Chem. Soc.*, **61**, 94 (1939). [g] Blicke and Monroe, *ibid.*, **61**, 92 (1939). [h] German Patent 617,536, *C. A.*, **30**, 731 (1936). [i] Knorr and Matthes, *Ber.*, **31**, 1069 (1898). [i] Mannich and Braun (*ibid.*, **53**, 1877 (1920)) found 172°. They prepared the hydrochloride also but merely stated that it is very hygroscopic. [k] With effervescence. [l] M. p. of chloroaurate.

Mannich and Braun[6] stated that the hydrochloride is hygroscopic; no melting point was reported by them.

Analysis of Amine Hydrochlorides.—We found the Fajans method[7] very suitable and advantageous for the determination of chlorine in many of our amine hydrochlorides. Since the method requires some modification in the case of an amine salt, the whole procedure is described below.

In order to carry out the analysis successfully the liberated amine must be extracted with ether. In the event that the amine base is very insoluble in water, ether can be added to the neutralized solution and titration performed without removal of the ether later. If the base is somewhat soluble, as is the case with methylcyclohexylmethylamine, the amine must be extracted and the ether layer removed, otherwise enough of the amine remains in the aqueous layer to obscure the end-point. When an amine was found to be very soluble in water it was so difficult to remove it completely from the water layer that the Fajans method was not used.

A mixture of the amine hydrochloride, which weighed 0.2–0.3 g., 15 cc. of water and one drop of phenolphthalein indicator was made alkaline with 2% chloride-free sodium hydroxide solution. If the amine hydrochloride is insoluble in water, sufficient alcohol may be added to effect solution or the alkali may be added in portions and the mixture agitated or warmed until the red color has disappeared before each addition of the alkali. The liberated amine is extracted three times with 50-cc. portions of ether, the ether layer removed carefully by decantation and the slight amount of solvent which remains can be evaporated on a steam-bath. The cold solution is neutralized with 1:50 nitric acid and diluted to about 75 cc. Ten drops of dichlorofluorescein indicator and 5 cc. of 2% dextrin solution are added and the solution titrated with 0.1 *N* silver nitrate. Calcd. for $C_{23}H_{38}NCl$ (benzyldi-β-cyclohexylethylamine hydrochloride): Cl, 9.75. Found: Cl, 9.73, 9.76.

(7) See Willard and Furman, "Elementary Quantitative Analysis," D. Van Nostrand Co., New York, 1935, p. 138.

Summary

A number of mixed amines of the general type CH_3NRR' have been described in which R and R′ represent alkyl, cycloalkylalkyl and arylalkyl groups. Eleven of the amines were found to be strong antispasmodics.[8]

(8) A very recent contribution to the field of antispasmodics is the paper by Buth, Külz and Rosenmund (*Ber.*, **72**, 19 (1939)).

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 2, 1939